REMARKS

The present response is being made during the second month following the three months statutorily provided for response. Enclosed please find a request to purchase an additional two months for response from December 5, 1997 to February 5, 1998 along with the necessary fee.

Applicants acknowledge the Examiner's remarks concerning informal drawings and request that the submission of formal drawings be delayed until after notice of allowance in the case.

In the Office Action the Examiner objected to the Specification because an abstract was not provided on a separate sheet as required by 37 CFR 1.72(b). The "Brief Description of the Drawings" was objected to because the description for Figure 2 did not adequately describe the four panels of the drawing. An apparent typographical error was cited in a reference citation on page 18. Applicants' attorney is attempting to contact the Examiner concerning the Abstract issue since Applicants' copy appears to have a conforming Abstract. This matter will be addressed in a Supplemental Amendment if necessary. The other matters have been addressed in the above amendments.

Claims 4, 8, and 11-12 were rejected under 35 U.S.C. § 112, second paragraph for indefinite phrases. The Examiner detailed the specific vague and indefinite phrases. Claims 4, 8, 11, 14, 15, 19, and 20 contained improper Markush groupings. Claims 12 and 20 have elements lacking antecedent basis. Claim 12 also lacks a step that completes the claim's preamble.

Claims 1-3, 5-7, and 9-10 were rejected under 35 U.S.C. § 102(b) as having been anticipated by **Jirkowski et al.** (*Histochemistry* 91:51). Claims 1-11 were rejected under 35 U.S.C. § 102(b) as having been anticipated by **Vanderlaan et al.** (U.S. Patent No. 5,053,336).

Claims 4, 8, and 11 were rejected under 35 U.S.C. § 103(a) as being unpatentable over **Jirkowski et al.** in view of **Vanderlaan et al.** Claims 12-15 and 17-20 were rejected as being unpatentable over **Gorcyzca et al.** (*Cancer Research* 53:1945-52) in view of **Vanderlaan et al.** Claim 16 was rejected under 35 U.S.C. § 103(a0 as being unpatentable over **Gorcyzca et al.** in view of **Vanderlaan et al.** and further in view of **Keydar et al.** (U.S. Patent No. 4,707,438). On the bottom of page 10 of the Office Action the Examiner begins to make a point concerning a rejection based on **Gorcyzca et al.** in view of **Jirkowski et al.** Unfortunately, the next page of Applicants' attorney's copy of the Office Action is unreadable. Perhaps the Examiner is suggesting possible allowance of a limited version of Claim 17. The Examiner has offered to fax a replacement page. When that page arrives, this matter will be address, if necessary, in a Supplemental Amendment.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph.

Applicants have amended the claims to correct the errors pointed out by the Examiner. Further, a few additional spelling and other errors have been corrected. Applicants believe that the claims are no longer indefinite and respectfully request withdrawal of the claim rejections under 35 U.S.C. § 112.

Claim Rejections Under 35 U.S.C. § 102

Applicants respectfully submit that there are significant differences between **Jirkowski et al.** and the present invention. **Jirkowski et al.** is directed towards a method of labeling short DNA probes *in solution* whereas the present invention is directed to labeling DNA *in situ* within a cell. Since the identity of the apototic cells is of utmost importance, it stands to reason that the present technique requires fixed cells so that cellular identity is preserved. Furthermore, apototic cells often have DNA that is so digested that a significant portion of the DNA will be lost if the cell is not stabilized with a cross-linking fixative. However, the original claims failed to point out this distinction. As now amended the claims are directed towards a method of labeling DNA *in situ*. There is no reason to suppose that a method useful for labeling DNA in solution would necessarily give satisfactory results on *in situ* DNA. Since **Jirkowski et al.** does not disclose the element of labeling *in situ* DNA, that reference cannot be said to anticipate the present invention. Applicants respectfully request the Examiner to withdraw the rejections under 35 U.S.C. § 102 based on **Jirkowski et al.**

In terms of the rejections under 35 U.S.C. § 102 based on **Vanderlaan et al.**, that reference describes using a living cell's synthetic machinery to incorporate halogenated nucleotides into the DNA of living cells. This DNA is necessarily double-stranded, and it is a well known fact that antihalogenated nucleic acid antibodies are unable to bind to double stranded DNA. Therefore, **Vanderlaan et al.** must include a DNA denaturation step to open up the double helix to allow the antibody to bind. This step is cumbersome and also tends to damage the cellular morphology. **Vanderlaan et al.** is used to pulse label cells to detect which cells were

in S-phase (i.e., this is an alternative to use of radioactive thymidine). The present invention is different because the labeling happens directly without a DNA denaturation step as is required in **Vanderlaan et al.**. However, the original "comprising" claim language did not specifically eschew a denaturation step. That oversight has now been remedied. Therefore, Applicants respectfully request the Examiner to withdraw the rejections of Claims 1-11 under 35 U.S.C. § 102 based on **Vanderlaan et al.**

Claim Rejections Under 35 U.S.C. § 103

In terms of the rejection of Claims 4, 8, and 11 as being unpatentable over **Jirkowski et al.** in view of **Vanderlaan et al.**, these claims are dependent claims. As argued above, the amended base claims from which Claims 4, 8, and 11 depend are not properly rejected under 35 U.S.C. § 102. Since these claims are not otherwise rejected, they should now be allowable as depending from an allowable base claim.

In terms of the rejections of Claims 12-15 and 17-20 under 35 U.S.C. § 103(a) as being unpatentable over **Gorcyzca et al.** in view of **Vanderlaan et al.** Applicants respectfully traverse the rejections and request reconsideration in light of the following. **Gorcyzca et al.** demonstrates the utility of using TdT to incorporate biotinylated or digoxygenin-labeled nucleotides into DNA as a way of detecting apotosis. As explained above, the prior art did not teach the use of halogenated nucleotides as a way of labeling natural strand breaks *in situ*. As is remarked in the specification, it is surprising that very few workers have appreciated the economic advantages of using halogenated nucleotides instead of biotinylated or digoxygenin-labeled nucleotides. In fact,

even today most molecular biologists persist in using the expensive digoxygenin method. Thus, although **Gorcyzca et al.** teaches that TdT can label strand breaks in apotosis, it does not teach or suggest the significant superiority of halogenated nucleotides. **Vanderlaan et al.** teaches the use of halogenated nucleotides but only for labeling with polymerase which leaves a double stranded label that requires DNA denaturation. In other words, there is no reason to connect the halogenated double strands of **Vanderlaan et al.** with the TdT created single strands of **Gorcyzca et al.** More important, however, is the significant superiority of the halogenated method (see Table 1, page 15). While one might select halogenated precursors for economic reasons, the data show that the sensitivity is twice that of the next best method (digoxygenin) and several times better than the other commonly used methods. Applicants submit that this represents unexpected and surprisingly superior results. There is nothing in the prior art to teach or suggest that such superiority would be attained with halogenated precursors as opposed to digoxygenin or other labels. Applicants are the first to discover this significant advantage and deserve patent protection as a result.

Additional Prior Art

The present attorney recently took over the case and was personally aware of the included publication by Szabo et al. (*Experimental Cell Research* 169 (1987) 158-68. The attorney believes that while this publication is related to the present invention, it does not render the present invention obvious. In the publication cells are labeled by simultaneous incubation with DNase I, TdT and BrdU-TP. This is exactly analogous to a true nick translation and indicates that cellular DNA (like purified DNA) can be subjected to nick translation. That TdT is capable of

labeling the numerous fresh strand breaks created by simultaneously present DNase I does not prove or even strongly suggest that TdT would work to label existing breaks caused by apotosis. Also, it does not teach or suggest the unexpected advantages (discussed above) yielded by incorporation of halogenated nucleotides for detecting apotosis.

Applicant respectfully submits that the case is now in condition for allowance and requests an early notification of the same. Questions, suggestions, and comments from the Examiner are welcomed. If the Examiner believes that a telephone conference would help further the prosecution of the case, the Examiner is requested to contact the undersigned attorney at the listed telephone number.

Respectfully submitted,

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